REMARKS

A check for the fee for a one month of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-3, 5, 6, 8, 10-35, 37-39, 41, 42, 44, 46 and 69-89 are pending in this application. Claims 1, 22 and 69 are amended for clarity. For example, the claims 1 and 22 are amended to reference antecedents in the claims. Claim 1 also is amended to emphasize that the LBD is modified. Claim 22, is rewritten as an independent claim. Claim 89 is added. Claim 89 is previously pending claim 7, which was inadvertently cancelled in the previous response. The Office Action indicated that claims 1-3, 5, 6, 8, 10-35, 37-39, 41, 42, 44, 46 and 69-89 were pending in this application. According the records of the undersigned, claims 1-3, 5, 6, 8, 10-35, 37-39, 41, 42, 44, 46 and 69-88 were pending. Claim 89 is added herein.

OBJECTION TO CLAIM 22

Claim 22 is objected to as allegedly being drawn to non-elected subject matter, and as being dependent upon a rejected base claim. A protein comprising a fusion protein of SEQ ID No. 1 has been elected and is deemed allowable.. Claim 22 is retained without amendment to permit rejoinder of non-elected species upon allowance of a generic claim As pending claim 22 includes species that are within the scope of claims 1-21 and 73-81. As evidenced below, all pending claims are novel and unobvious and, hence, should be allowable. All species in claim 22 that are within the scope of allowable claims should be rejoined and allowed. Hence, any non-elected subject matter is retained for possible rejoinder pending a determination of allowance of generic claims.

THE REJECTION OF CLAIMS 1-3, 5-35, 37-46, 69 and 73 UNDER 35 U.S.C. §102(b)

Claims 1-3, 5-21, 23, 24, 26-46, 69 and 73 are rejected under 35 U.S.C. §102(b) as being anticipated by Scheller *et al.* (J. Biol. Chem. 273(37):24216-22 (1998)) because Scheller *et al.* discloses chimeric fusion proteins combining amino terminal, DNA binding and ligand binding domains of the androgen and glucocorticoid receptors (AR, GR). It further is alleged that the ligand binding domain of the fusion proteins in Scheller *et al.* are modified to change ligand specificity from the native receptor because the ligand binding domains of AR and GR are interchanged. These fusion proteins allegedly meet the

limitations in independent claim 1. The Examiner further alleges that Scheller discloses all the additional limitations in dependent claims 2, 3, 5-7, 9-19, 69 and 73. Independent claim 8 is allegedly anticipated because the chimeric proteins of Scheller comprise C2H2 domains in the zinc finger region of the nucleotide binding domain. Independent claim 20 is allegedly anticipated because the chimeras of Scheller *et al.* are ligand activated transcriptional regulators. Dependent claim 21 is allegedly anticipated because "there is no structural limitation on 'derivatives' the repression domains. Claims 23, 24 and 26-31 are rejected because Scheller *et al.* allegedly discloses nucleic acid encoding the chimeric proteins. Claims 32-38 are rejected because the vectors of Scheller *et al.* allegedly were constructed using viral vectors. Claims 39-46 are rejected because Scheller *et al.* allegedly discloses the transfection of cells with nucleic acids encoding chimeric receptors and hormone response elements upstream of reporter genes. This rejection is respectfully traversed.

The independent claims

Claim 1 requires the following elements:

1) it is directed to a fusion protein that contains two domains:

a nucleotide binding domain (DBD) and a modified ligand binding domain (LBD);

2) the fusion protein is a ligand activated transcriptional regulator (*i.e.*, the fusion protein regulates transcription of a targeted sequence of nucleotides and such regulation is activated by a ligand that interacts with the LBD);

2) the DBD:

is a polydactyl zinc-finger;

it contains ***at least three*** modular portions of a polydactyl zinc finger;

each modular portion interacts with a contiguous sequence of nucleotides of at least about 3 nucleotides (*i.e.*, three modular portions interact with at least 9 nucleotides so that the fusion protein recognizes at least 9 contiguous nucleotides); and

3) the LBD

the LBD is from an intracellular receptor;

the LBD is modified so that *its* specificity for endogenous and exogenous ligands is different from the specificity of the ligand binding domain of the native hormone receptor (*i.e.*, if the native receptor is an estrogen receptor and the LBD is

derived from an estrogen receptor, the LBD is modified so that the fusion protein is not activated by estrogen; hence the binding specificity of the LBD is changed).

Claim 32

Claim 32 is directed to a viral vector comprising a sequence of nucleotides encoding a fusion protein. The fusion protein contains a DBD operatively linked to an LBD domain from an intracellular receptor. The DBD is a polydactyl C2H2 zinc-finger peptide or modular portion thereof that interacts with a contiguous nucleotide sequence of at least about 9 nucleotides (*i.e.* contains at least three modular portions); and the fusion protein is a ligand activated transcriptional regulator.

Rejected dependent claims recite additional details. In this instance, as discussed below, Scheller does not disclose all limitations recited in independent claim 1 or claim 32. Therefore, Scheller *et al.* does not disclose all elements of any of the dependent claims.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed subject matter is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Differences between the disclosure of Scheller *et al.* and the rejected claims

Scheller *et al.* discloses chimeric receptors designed to test the roles particular domains play in activity. The chimeras were constructed from the mouse androgen receptor (mAR) and the rat glucocorticoid receptor (rGR). Each receptor was divided into three cassettes encompassing the N-terminus, DBD, and LBD. Each chimera constructed (see, Figure 1) is named from the N-terminus by the letter of origin for a particular domain. Hence GAA refers to a chimeric receptor that includes the N-terminus from rGR, and the DBD and LBD from mAR. None of the constructs contained more than one LBD or DBD and none contain an LBD that is modified so that its ligand specificity is changed The ligand

specificity of LBD domains employed in the contracts of Scheller et al. are not modified but retain the specificity that they had in the native receptor. The truncation in the ligand binding domain in chimeras disclosed by Scheller *et al.* only results in a change in cooperative receptor interaction and DNA binding by the DNA binding domain, but does not change ligand specificity.

Thus, Scheller *et al.*, **does not disclose at least two requite** elements of all of the pending claims: (1) the requirement that the DBD include at least three zinc finger modules; and (2) that the ligand specificity of the LBD is modified.

(1) As discussed and shown in the previous response, the DBD from each of the GR and AR receptors contains *two* zinc finger modules (*i.e.* the fusion protein recognizes 6 contiguous nucleotides). None of the constructs disclosed by Scheller *et al.* contains more than one DBD . Hence the chimeric receptors disclosed by Scheller *et al.* contain only *two zinc finger modules* that recognize 6 contiguous nucleotides.

Therefore, Scheller *does not* disclose a fusion protein that contains at least *three* zinc fingers as required by the instant claims, since the AR and the GR DNA binding domains contain *two* zinc fingers (modules). Thus, Scheller *et al.* which discloses chimeric receptors that contain only *two* zinc finger modules, cannot anticipate claim 1 nor any of the pending claims, which all require that the fusion protein (or encoded protein) contain (or encode) at least three zinc fingers.

(2) Furthermore, Scheller *et al.* discloses fusion proteins in which the ligand specificity of the LBD portion is **not** modified compared to its specificity in the native receptor. The ligand specificity of the LBDs in the chimeric receptors of Scheller *et al.* is not changed; they interact with the same ligands with which they interact in the native receptors. Changing the ligand binding domain of AR with GR or vice versa is not the same as altering the binding specificity of the AR or GR LBD. Each domain retains its ligand specificity. Interchanging AR with GR or *vice versa* does not meet the requirement for a modified LBD of the instant claims. The instant claims require that the fusion protein include a modified LDB. It is modified to have altered ligand specificity compared to the specificity of the LDB in the native receptor from which the LBD is derived. Modification of the LBD means that these fusion proteins are not substantially activated by the ligands that activate the endogenous receptor permitting their activation to be more targeted.

Analysis

Thus the chimeric receptors of Scheller *et al.* do not contain at least *three* zinc finger modules nor a modified LBD as required by the instant claims. Therefore, since anticipation requires disclosure of all elements as claimed, Scheller *et al.* cannot anticipate claim 1 nor any claim dependent thereon.

Rebuttal to statements of the Examiner

The Examiner points to Figure 1 page 24218 stating that Scheller *et al.* provides various combinations of the amino terminal, DBD and LBDs of the AR and GR receptor. The Examiner urges that this meets the limitation of claims 1 and 69. Claims 1 and 69, however, require at least three zinc finger modules. None of the chimeric receptors described in Scheller *et al.* include more than one LBD from an AR and GR receptor. As discussed above and demonstrated in the previous response, the AR and GR receptor DNA binding domains contain two zinc fingers, which have a C4H4 C4 zinc-finger motif (see, *e.g.*, Liden *et al.* (1997) J. Biol. Chem. 272:21467-21472, at, for example, page 21467, col.1; Hard *et al.* (1990) Science 249:157-160, copies provided with the response mailed March 26, 2004). Each of these LBDs and chimeric receptors contains only two zinc fingers. Thus, none of chimeras disclosed by Scheller *et al.* includes an LBD that contains at least *three* zinc finger modules.

Therefore Scheller et al. does not and cannot anticipate claim 1 nor any claims dependent thereon. Similarly, claim 32, which requires that the viral vector encode a fusion protein that contains at least three zinc finger modules, cannot be anticipated by Scheller *et al.*

THE REJECTION OF CLAIMS 1-3, 5, 6, 8, 10-21, 23-35, 37-39, 41, 42, 46 and 69-89 UNDER 35 U.S.C. §103(a)

Claims 1-3, 5, 6, 8, 10-21, 23-35, 37-39, 41, 42, 46 and 69-89 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Scheller *et al.* (1998) in view of Sibson *et al.* (WO/9401548) because Scheller *et al.* allegedly teaches the claimed fusion proteins but does not teach non-viral vectors. It is further alleged that Sibson *et al.* teaches the use of non-viral vectors and cells to express DNA, as well as methods for producing proteins. The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the teachings of Sibson *et al.* by substituting a cDNA in the polycloning region of the vector with the polynucleotide (cDNA) of Scheller *et*

al. for the purpose of transfecting a host cells as taught by Sibson *et al.* in view of the suggestion in Sibson *et al.* that it would be desirable to do so (pages 8-13). The Examiner asserts that one of ordinary skill in the art would have been motivated to make this substitution in order to express the protein encoded by the introduced DNA in a host cell to perform ligand binding and functional assays. The Examiner further asserts that one of ordinary skill would have had a reasonable expectation of success since Sibson *et al.* allegedly teaches that these techniques are widely used in the art and are highly successful (Sibson *et al.*, page 10, line 38-page 12, line 42).

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v. Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

Claims

Independent claims 1 and 32 are discussed above. If the independent claims are not rendered obvious by the combined teachings of a cited reference, dependent claims cannot be obvious.

Analysis

Teachings of the cited references and differences from the instant claims

Scheller *et al.*

As discussed above, Scheller *et al.* does not teach or suggest a fusion protein containing at least three zinc fingers, nor a fusion protein that contains a ligand binding domain that has been modified to change its ligand specificity. Scheller *et al.* teaches combining a ligand binding domain that retains its native ligand specificity (such as the ligand binding domain of AR) with a nucleotide binding domain and/or N-terminus from a different hormone receptor (such as the DNA binding domain of GR). Changing the ligand binding domain of AR with GR or vice versa does not meet the limitation of claim 1. The AR ligand binding domain still possesses its native specificity.

Further, as noted above, Scheller *et al.* teaches chimeric proteins containing either androgen (AR) or glucocorticoid (GR) DNA binding domains. Androgen (AR) and glucocorticoid (GR) DNA binding domains contain two C4 zinc-finger peptides, not at least three as required by the instant claims. Thus, Scheller *et al.* does not teach or suggest a fusion protein that contains at least three modular at least three modular portions of a polydactyl zinc-finger (claim 1). Since the AR and GR contain C4 zinc-finger modular units, it does not teach fusion proteins with units from a C2H2 zinc-finger peptide as required by claim 32.

Thus Scheller *et al.* fails to teach or suggest elements of claim 1 and claim 32 including the required inclusion of at least three zinc fingers and modification of the LBD to alter its specificity for exogenous and endogenous ligands compared to the receptor from which the LBD is obtained. With respect to claim 32 Scheller *et al.* fails to teach or suggest a viral vector nor nucleic acid encoding a fusion protein that includes a DBD that contains zinc fingers with a C2H2 motif.

Sibson *et al.*

Sibson *et al.* fails to cure these deficiencies. Sibson *et al.* is directed to nucleic acid fragments isolated from brain adrenal tissue, placenta or bone marrow and to the use of such

fragments. Sibson *et al.* teaches the incorporation of such nucleic acid fragments into an *E. coli* plasmid vector and transformation of *E. coli* cells for expression of corresponding proteins. Sibson *et al.* also teaches that corresponding monoclonal or polyclonal antibodies to these proteins can be prepared.

Sibson *et al.* does not teach or suggest any transcriptional regulatory proteins nor any fusion proteins that contain at least at least three modular portions of a zinc finger and include a modified LBD. Specifically, Sibson *et al.* does not teach or suggest preparation of a any ligand activated transcriptional regulators, nor does it teach or suggest the use of at least three zinc finger modules in such regulators, Further, Sibson *et al.* does not teach or suggest DNA binding domains containing C2H2 zinc-finger peptides (claim 32). Thus, Sibson *et al.* does not cure the deficiencies in the teachings of Scheller *et al.*

The combination of teachings of Scheller *et al.* with those of Sibson *et al.* does not result in any of the claimed products

First it is noted that Sibson *et al.* and Scheller *et al.* are not analogous art, and, are not properly combinable. Sibson *et al.* provides an *E. coli* cloning vector and Scheller *et al.* provides AR-GR chimeric receptors. There is no suggestion in either reference that would have lead one of ordinary skill in the art to have combined their teachings. Notwithstanding this, even upon combination, the combination does not result in the instantly claimed fusion proteins, nucleic acid molecules and vectors. . As discussed above, Scheller *et al.* teaches fusion proteins that contain only two modular units and LBDs with native specificity. Scheller *et al.* does not teach or suggest fusion proteins with at least three modular units nor alterations in LBD specificity. In fact, Scheller *et al.* is directed to a study designed to test the roles particular domains play in activity and constructs the chimeras to assess these activities. Hence, not only does Scheller *et al.* not teach modifications of the LBD, it provides no suggestion for doing so. The ligand binding domain in the chimeric receptors of Scheller *et al.* retains its native ligand specificity.

Sibson *et al.* does not cure the deficiencies of Scheller *et al.* Sibson *et al.* does not teach or suggest ligand activated transcriptional regulators nor substitution of three zinc finger modules for two zinc finger modules in the AR and GR receptors of Scheller *et al.* nor does Sibson *et al.* suggest substituting the C4 motif of the DBD of the GR and AR receptors with a C2H2 motif (as required by claim 32 and dependents). Further Sibson *et al.* does not teach or suggest modifying a ligand binding domain of a hormone receptor to change its

ligand specificity compared to the native hormone receptor from which the ligand binding domain originates.

Therefore, the combination of teachings of the references does not result in the instantly claimed subject matter. With respect to all claims, neither reference, singly nor in any combination thereof teaches or suggests employing *three* zinc finger modules to bind to and recognize at least 9 contiguous nucleotides rather than 6. None of the cited references, singly nor in any combination thereof teaches or suggests modification of the LDB to alter specificity for exogenous and endogenous ligands. With respect to claim 32 and dependent claims, none of the cited references, singly nor in any combination, teaches or suggests selection of a C2H2 motif in place of the C4 motif. Therefore, the combination of teachings of the cited references does not result in any of the products of the instant claims. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,

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